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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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WOMBLE CARLYLE SANDRIDGE & RICE, PLLC
ATTN: PATENT DOCKETING 32ND FLOOR
P.O. BOX 7037
ATLANTA, GA 30357-0037

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FLOOD, MICHELE C	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/692,105	BRADLEY ET AL.	
	Examiner	Art Unit	
	Michele Flood	1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 April 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Acknowledgment is made of the receipt and entry of the amendment filed on April 9, 2007 with the cancellation of Claims 25-53.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-24 are under examination.

Response to Arguments

Claim Rejections - 35 USC § 112

Claims 8-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The rejection stands for the reason set forth in the previous Office action and for the reason set forth herein.

Applicant argues that based on the particular language of the preamble of original Claim 1, the rejection is moot. Applicant's assertion was fully considered but not found persuasive. Thus, with regard to Claims 8-10 and 14, the claims are not set forth in terms of a positive statement; and, therefore, the metes and bounds of the claim limitations are uncertain. This rejection is made with particular regard to Claim 8, wherein Applicant directs the instantly claimed invention to "wherein the plasminogen is cleaved in the presence of at least one excipient that is an omega-amino acid"; as well as Claim 9, wherein Applicant directs the instantly claimed invention to "wherein the plasminogen is cleaved in the presence of at least one omega-amino acid selected from

the group consisting of lysine, epsilon amino caproic acid, tranexamic, poly lysine, arginine, and combinations thereof" because it is uncertain as to the subject matter to which Applicant intends to seek patent protection. Applicant should amend the claims to read on a positive step.

All other cited claims depend directly or indirectly from rejected claims and are, therefore, also, rejected under U.S.C. 112, second paragraph for the reasons set forth above.

Claim Rejections - 35 USC § 102

Claim1 -3, 8-15 and 18-23, as amended, remain rejected under 35 U.S.C. 102(b) as being anticipated by Robbins et al. (D24, Robbins, K C et al., The Journal of Biological Chemistry (1963), 238: 952-962. Purification of human plasminogen and plasmin by gel filtration on Sephadex and chromatography on Diethylaminoethyl-Sephadex.). Applicant's argument's have been fully considered but not found persuasive for the reason set forth in the previous Office action and for the reason set forth herein.

Applicant argues that Robbins fails to disclose any step involving an "active plasmin-specific absorbent material"; and, therefore, Robbins fails to anticipate the instantly claimed subject matter. However, Applicant's argument is not found persuasive because Robbins teaches a method for preparing plasmin comprising the instantly claimed process steps. For example, the plasmin taught by Robbins is prepared by activation of the proenzyme with trace quantities of urokinase in glycerol,

and isolation in a high state of purity by chromatography on DEAE-Sephadex™ columns. On page 956, Column 1, line 22 to page 957, Column 2, line 9, Robbins teaches complete conversion of plasminogen to plasmin with trace quantities of urokinase in a system containing 25% glycerol, 0.01M phosphate, and 0.034 glycine at pH 7.4. After activation, the plasmin was precipitated at pH 6.2 ± 0.2 with NaH_2PO_4 and dissolved in 0.005 N HCl; and, dialyzed at pH 3.7 followed by drying from the frozen state is taught as an alternative method. Robbins also teaches a method for further purification of plasmin by chromatography on DEAE-Sephadex™. For example, after isoelectric precipitation, the urokinase-activated plasmin was dissolved in 0.05M Tris-0.02 M lysine-0.1M NaCl buffer, pH 9.0, and dialyzed against 10 volumes of this buffer. Then, the enzyme was chromatographed on DEAE-Sephadex™. The pool was adjusted to pH 3.7 with N HCl and dried from the frozen state. The dried enzyme preparation was dissolved in a small volume of 50% glycerol. Robbins teaches, "The solution contained 73.3 units per ml and 3.7 mg of protein per ml." *See* page 956, Column 2, lines 54-55. On page 957, Column 1, lines 6-10, Robbins teaches, "Urokinase cannot be detected by enzymatic methods in any of the plasmin preparations." With regard to the claim limitation of "a reversibly inactive, acidified plasmin", Robbins teaches measuring plasmin activity of the referenced fibrinolytic composition using an adapted caseinolytic assay performed at a pH of 7.4, on page 952, Column 1, line 24 to Column 2, line 28; and, on page 962, Column 1, lines 40-42, Robbins teaches that the prepared plasmin had a specific activity of 21.4 casein units per mg of protein or 140 casein units per mg of nitrogen. Moreover, on page 958,

Column 2, lines 1-3, Robbins expressly teaches a purified plasmin solution in a pH 2.9 glycine buffer. With particular regard to the claimed subject matter, on page 958, Column 2, lines 15-17, Robbins expressly teaches a purified plasmin (No. 47) in 0.001 N HCl containing 0.1 M NaCl, ph 2.8, at 20°, which appears to be one and the same fibrinolytic composition disclosed and instantly claimed by Appellant. With regard to the claim limitation of "wherein the composition is a solution suitable for pharmaceutical use that can be raised to physiological pH by adding no more than about 5 volumes of serum to the solution relative to the volume of solution", as set forth in independent Claims 1 and 20, the Office finds that the fibrinolytic composition taught by Robbins is a solution suitable for pharmaceutical use, since there is nothing contained therein the Robbins' composition to preclude pharmaceutical use thereof the referenced composition, that can be raised to physiological pH by adding no more than about 5 volumes of serum to the solution relative to the volume of solution, as evidenced by the following calculations set forth in the table and assumptions presented below, which are based on the teachings set forth in the following website article: http://www.lakesidepress.com/pulmonary/books/physiology/chap7_1.htm, Chapter 7: Acid-Base Balance.

1. Serum is plasma with the fibrinogen removed by precipitation. Plasma is blood with the cells removed. Hence, serum is blood with both cells and fibrinogen removed. Accordingly, serum will be treated as if it was blood for the pH calculations. The only buffer of significance in blood is H2C03.

2. The article (http://www.lakesidepress.com/pulmonary/books/physiology/chap7_1.htm, Chapter 7: Acid-Base Balance) gives the normal physiological pH range as 7.3-7.52. It is reasonably assumed that the serum starts at a physiological pH and ends in a physiological pH as required by the claims. This sets the upper and lower bounds for the pH start and finish as these values.
3. The Office used the Henderson-Hasselbach equation, Eqn 7-2, to calculate the [HCO3] at each pH assuming that the blood gas remained constant at 40 torr (reasonable since the dilution is rapid).
4. Assuming that all of the plasmin to be titrated is in the acid form to start with and assuming that all of it is fully titrated by the serum, the change in [HCO3] is how much is titrated.
5. For convenience of calculation, the Office chose the volume of serum to be 1.0 liter, and the maximum volume of the plasmin to be titrated to be 0.2 L.
6. Therefore V1*M1=V2*M2, V1=1, V2=0.2, thus M1/V2=M2, the concentration of the buffer to be titrated. Our calculations show the maximum concentration of the buffer to be titrated at different starting pH values for the serum, as presented in the table below.

pH	$[H^+]$ nM	pCO2 torr	[HCO3] mEq/L	Change mEq/L	[.2V Plasmin] mEq/L
7.3	50	40	19.0	0.0	0.0
7.35	45	40	21.3	2.3	11.6
7.4	40	40	23.9	4.9	24.6
7.45	35	40	26.9	7.8	39.2
7.52	30	40	31.6	12.5	62.7

Thus, the range of concentration for the plasmin acid that can be titrated with no more than five volumes of serum and maintain the pH in physiological values is in the range of 0.0-62.7 mEq/L.

Now, we look to the teachings of Robbins et al. (1963). Acidified plasmin (No. 47) in 0.001 N HCl, ~pH of 2.8, is used in the sedimentation analysis at page 958, column 2, last paragraph. This is equal to 1 mEq of acid and hence, well with the range of plasmin acid that can be titrated, unless the initial pH of the serum is at the lower bound of 7.3. Even at a slightly higher pH value of 7.35, the serum has sufficient capacity to neutralize the amount of acid in the acidified plasmin taught by Robbins.

The reference anticipates the claimed subject matter.

Claim Rejections - 35 USC § 103

Claims 1-4 and 8-23, as amended, remain rejected under 35 U.S.C. 103(a) as being unpatentable over Robbins et al. (D24) in view of Sherry (D25, Sherry, S. J. Amer. Coll. Cardiol. (1989). The origin of thrombolytic therapy.), Castellino et al. (D9, Castellino, FJ et al. Meth. Enzymology (1981), 80: 365-378. Human plasminogen.), Morii et al. (N, EP 0256836 A1) and Wiman (D27, Wiman, B. Biochem. J. (1980), 191(1): 229-232. Affinity-chromatographic purification of human alpha 2-antiplasmin.). The rejection stands for the reasons set forth in the previous Office action and for the reasons set forth herein.

Applicant's arguments have been fully considered but they are not deemed persuasive because the cited references provide the suggestions and motivation to the claimed invention.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). For instance, Applicant argues that Robbins fails to disclose any step involving an "active plasmin-specific absorbent material"; and, therefore, Robbins fails to anticipate the instantly claimed subject matter. However, Applicant's argument is not found persuasive. In this case,

the primary teachings of Robbins were relied for the reason set forth in the previous Office and for the reason set forth herein. Because Robbins does not teach a method for preparing plasmin wherein the plasminogen activator is either streptokinase or tPA; wherein the plasminogen is soluble streptokinase; and, wherein the plasminogen activator is immobilized on a solid support medium comprising SEPHAROSE™, the secondary teachings of Sherry, Castellino, Morii and Wiman were relied upon. Firstly, both Sherry and Castellino, like Robbins, teach that streptokinase can activate plasminogen to plasmin. Moreover, on page 1091, Column 1, lines 29-33, Sherry teaches recombinant tPA as a plasminogen activator. Secondly, Morii teaches tissue plasminogen activator (tPA) as a plasminogen activator. Thirdly, Wiman teaches a method for purifying plasminogen to plasmin comprising activation of plasminogen to plasmin with SEPHAROSE™ -bound urokinase, on page 229, lines 29-31. At the time the invention was made, one of ordinary skill in the art would have been motivated and one would have had a reasonable expectation of success to modify Robbins' method of making plasmin by adding and/or replacing the process steps and/or ingredients to provide the claimed invention because Sherry teaches that the knowledge of streptokinase as an plasminogen activator to yield plasmin is well established in the history of thrombolytic therapy; with regard to streptokinase, Castellino teaches, "Once formed, the activator complex activates human plasminogen in a similar fashion to urokinase", on page 1091, Column 1, lines15-17; Robbins teaches, "High purity plasmin can be prepared from Kline method plasminogen by activation with streptokinase, on page 952, Column 1, lines 7-9; Morii teaches that tPA made by his method is free of

impurities and the activity of the tPA is unchanged; and, finally, the method of purifying plasminogen with SEPHAROSE™-bound urokinase taught by Wiman would have provided a one step method for the activation and purification of plasminogen to plasmin by modifying the Robbins' method, which would save time and reduce production cost of the composition.

Moreover, it would have been obvious to one of ordinary skill in the art at the time the invention was made to add the claimed ingredient in the making of the claimed composition and method because it is well known that its *prima facie* obvious to combine two or more ingredients each of which is taught by the prior art to be useful for the same purpose in order to form a third composition which is useful for the same purpose. The idea for combining them flows logically from their having been used individually in the prior art. *In re Pinten,* 459 F. 2d 1053, 173 USPQ 801 (CCPA 1972); *In re Susi,* 58 CCPA 1074, 1079-80; 440 F.2d 442, 445; 169 USPQ 423, 426 (1971); *In re Crockett,* 47 CCPA 1018, 1020-21; 279 F.2d 274, 276-277; 126 USPQ 186, 188 (1960). Thus, at the time the invention was made, one of ordinary skill in the art would have been motivated and one would have had a reasonable expectation of success to replace one ingredient for the other because the claimed invention is no more than the substitution of known ingredients, one for the other, which have the same functional effect for the purification of a plasmin from plasminogen; and the claimed process step is no more than the replacement of a two-step process with a one-step process step. Thus, the claim limitations are no more than an arbitrary matter of experimental design choice to result the purification of a product.

Accordingly, the claimed invention was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, especially in the absence of evidence to the contrary.

Claims 1-5 and 8-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Robbins et al. (D24), Sherry (D25, Sherry, S. J. Amer. Coll. Cardiol. (1989). The origin of thrombolytic therapy.), Castellino et al. (D9, Castellino, FJ et al. Meth. Enzymology (1981), 80: 365-378. Human plasminogen.), Morii et al. (N, EP 0256836 A1) and Wiman (D27, Wiman, B. Biochem J. (1980), 191(1): 229-232. Affinity-chromatographic purification of human alpha 2-antiplasmin.) in view of Silver et al. (P1, IS 6,479,253 B1), Yago et al. (P3, US 5,879,923) and Diedrichsen et al. (P18, US 4,462,980).

The rejection stands for the reasons set forth in the previous Office action and for the reasons set forth herein.

Applicant's arguments have been fully considered but they are not deemed persuasive because the cited references provide the suggestions and motivation to the claimed invention.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in

the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In the instant case, the combined teachings of Robbins, Sherry, Castellino, Morii and Wiman were relied upon for the reason set forth above. The combined teachings as set forth immediately above taught the claimed method except for the instantly claimed ingredients. Therefore, the teachings of Silver, Yago and Diedrichsen were relied upon because they taught that the instantly claimed process ingredients were beneficial in the preparation of plasmin composition, as evidenced by the teachings Silver, Yago and Diedrichsen. Firstly, Silver teaches a method of purifying a serine protease (note that plasmin is a serine protease) comprising binding the serine protease to a column comprising p-aminobenzamidine crosslinked to SEPHAROSE™ beads, in Column 30, lines 29-42. In Column 22, lines 35-42, Silver also teaches that purification of proteins, such as the serine proteases, by affinity chromatography, ion exchange chromatography, filtration chromatography, hydrophobic interaction chromatography, gel filtration chromatography, *etc.*, are standard protein purification techniques. Secondly, Yago teaches compositions comprising plasmin and the following (B-1): an oligopeptide comprising at least two amino acids bonded to each other, where the two amino acids are selected from the group consisting of lysine, arginine, glycine, alanine, aspartic acid and methionine; (B-2): at least two amino acids selected from the group consisting of lysine, arginine, glycine, alanine, aspartic acid and methionine; or (B-3): an amino acid selected from the group consisting of lysine, arginine, glycine, alanine, aspartic acid and methionine and a polyhydric alcohol. Yago teaches that the combining of plasmin with

any of the components of either (B-1), (B-2) or (B-3) stabilizes the activity of plasmin. Thirdly, in Column 2, line 62 to Column 3, lines 33, Diedrichsen teaches stabilizing plasmin compositions with polyhydroxy compounds, such as sugars and sugar alcohols, as well as glycerol. For example, in Column 7 under "Example 1", Diedrichsen teaches a method of making a stable solid formulation of active plasmin wherein the pH is adjusted to 3.0 Diedrichsen also teaches a method of admixing the plasmin preparations with labeled glucose technetium-99m at pH 2.0-4.0. *See* Column 6, lines 14-19. At the time the invention was made, one of ordinary skill in the art would have been motivated and one would have had a reasonable expectation of success to modify the method of making the composition taught by the combined teachings Robbins, Sherry, Castellino, Morii and Wiman by adding the instantly claimed ingredients to provide the claimed invention because Silver teaches that the purification of serine proteases, such as plasmin, by benzamidine comprising absorbent material and hydrophobic interaction chromatography is well-established and well-known; Yago teaches that plasmin comprising plasmin in combination with an additional component, such as, 1) an oligopeptide comprising at least two amino acids, or 2) at least two amino acids, or 3) a single amino acid and a polyhydric alcohol provides a stable plasmin for a long time; and, finally, Diedrichsen teaches adding polyhydric compounds, such as sugars and sugar alcohols, and glycerol to acidified plasmin compositions as stabilizing agents to impede the aggregation of plasmin and thus the denaturation of the composition thereof.

Moreover, it would have been obvious to one of ordinary skill in the art at the time the invention was made to add the claimed ingredients in the method of making the claimed composition because it is well known that its *prima facie* obvious to combine two or more ingredients each of which is taught by the prior art to be useful for the same purpose in order to form a third composition which is useful for the same purpose. The idea for combining them flows logically from their having been used individually in the prior art. *In re Pinten,* 459 F. 2d 1053, 173 USPQ 801 (CCPA 1972); *In re Susi,* 58 CCPA 1074, 1079-80; 440 F.2d 442, 445; 169 USPQ 423, 426 (1971); *In re Crockett,* 47 CCPA 1018, 1020-21; 279 F.2d 274, 276-277; 126 USPQ 186, 188 (1960).

Accordingly, the claimed invention was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, especially in the absence of evidence to the contrary.

Claims 1-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Robbins et al. (D24), Sherry (D25, Sherry, S. J. Amer. Coll. Cardiol. (1989). The origin of thrombolytic therapy.), Castellino et al. (D9, Castellino, FJ et al. Meth. Enzymology (1981), 80: 365-378. Human plasminogen.), Morii et al. (N, EP 0256836 A1) and Wiman (D27, Wiman, B. Biochem J. (1980), 191(1): 229-232. Affinity-chromatographic purification of human alpha 2-antiplasmin.), Silver et al. (P1, IS 6,479,253 B1), Yago et al. (P3, US 5,879,923) and Diedrichsen et al. (P18, US 4,462,980) in view of Trese et al. (A) and Hiemstra et al. (N). The rejection stands for the reasons set forth in the previous Office action and for the reasons set forth herein.

Applicant's arguments have been fully considered but they are not deemed persuasive because the cited references provide the suggestions and motivation to the claimed invention.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In the instant case the combined teachings of Robbins, Sherry, Castellino, Morii, Wiman, Silver, Yago and Diedrichsen are set forth above. The combined teachings as set forth immediately above taught the claimed method except for the instantly claimed process step. However, it would have been obvious to one of ordinary skill in the art to add the instantly claimed process step to the modified method for preparing plasmin taught by the combined teachings of Robbins, Sherry, Castellino, Morii, Wiman, Silver, Yago and Diedrichsen to provide the instantly claimed invention because at the time the invention was made it was known in the art that the instantly claimed process step was beneficial in the purification of a plasmin composition, as evidenced by the teachings of Trese and Hiemstra. Firstly, Trese teaches a method for making a plasminogen from blood plasma comprising binding plasminogen to an activated affinity cartridge containing lysine, contacting the absorbent material with an elution buffer containing episilon-

aminocaproic acid, and releasing the bound plasminogen from the affinity cartridge by injecting an elution buffer containing episilon-aminocaproic acid into the affinity cartridge. Trese further teaches cleaving the purified plasminogen in the presence of streptokinase to yield an active plasmin and further subjecting the plasmin to nanofiltration, wherein the nanofiltration is carried out using a filter membrane having an average pore size of 10 to about 30 nm, preferably 15 nm. Secondly Hiemstra teaches a method for removing viruses from a protein solution comprising subjecting the solution to a prefiltration step to remove large proteins and subjecting the resulting product to nanofiltration which removes viruses. On page 5, lines 11-21, Hiemstra further teaches that the prefiltration step removes high molecular weight contaminants, such as fibrinogen, from a blood derived protein solution; and, on page 4, lines 22-27, Hiemstra teaches that the step of nanofiltration is carried out over a nanofilter having a cut-off value of between about 10 to about 30 nm, preferably 15 nm to remove disease-causing viruses. At the time the invention was made, one of ordinary skill in the art would have been motivated and one would have had a reasonable expectation of success to add a further process step comprising nanofiltration of the plasmin solution taught by the combined teachings of the aforementioned references to provide the instantly claimed invention because both Trese and Hiemstra taught that nanofiltration of blood derived products removed disease causing viruses from blood products and provided a blood-derived product that is safe for human administration for therapeutic purposes. Thus, the claim limitations are no more than an arbitrary matter of experimental design choice to provide a result effect variable for the purification of a product.

Accordingly, the claimed invention was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, especially in the absence of evidence to the contrary.

Claims 1-3, 5-15 and 18-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Robbins et al. (D24) in view of Silver et al. (P1, IS 6,479,253 B1), Trese et al. (A*), Hiemstra et al. (N) and Diedrichsen et al. (P18, US 4,462,980). The rejection stands for the reasons set forth in the previous Office action and for the reasons set forth herein.

Applicant's arguments have been fully considered but they are not deemed persuasive because the cited references provide the suggestions and motivation to the claimed invention.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In the instant case, the primary reference of Robbins was relied upon for the reasons set forth in the previous Office action and for the reason set forth herein. Robbins taught the instantly claimed invention except for wherein the plasminogen is further removed by hydrophobic

interaction; wherein the plasminogen is further removed by hydrophobic interaction; further comprising nanofiltration of the plasmin solution wherein the nanofiltration is carried out using a filter membrane characterized by an average pore size of approximately 15 nm; and, further including stabilizing the reversibly inactive acidified plasmin by adding a sugar or sugar alcohol selected from the group consisting of glucose, maltose, mannitol, sorbitol, sucrose, lactose, trehalose, and combinations thereof. Therefore, the seconday teachings of Silver, Trese, Hiemstra and Diedrichsen were relied upon because they taught that the instantly claimed process steps and ingredients were known in the art to be beneficial in the making of a plasmin. Given the foregoing, one of ordinary skill in the art would have been motivated and one would have had a reasonable expectation of success to add the instantly claimed process steps and ingredients to the method of purifying a plasmin taught by Robbins to provide the instantly claimed method because at the time the invention was made Silver taught a method of preparing a serine protease (note that plasmin is a serine protease) comprising binding the serine protease to a column comprising p-aminobenzamidine crosslinked to SEPHAROSE™ beads, in Column 30, lines 29-42; and, in Column 22, lines 35-42, Silver also teaches that purification of proteins, such as the serine proteases, by affinity chromatography, ion exchange chromatography, filtration chromatography, hydrophobic interaction chromatography, gel filtration chromatography, *etc.*, are standard protein purification techniques; both Trese and Hiemstra taught that nanofiltration of blood derived products removed disease causing viruses from blood products and provided a blood-derived product that is safe for

human administration for therapeutic purposes, wherein the nanofiltration was carried out using a filter membrane filter characterized by an average pore size of approximately 15 nm; and, Diedrichsen taught that the addition of polyhydric compounds, such as sugars and sugar alcohols, and glycerol to acidified plasmin compositions stabilize the acidified plasmin product and impedes aggregation of the plasmin composition; and, thus the denaturation of the composition. Thus, the claim limitations would have been no more than an arbitrary matter of experimental design choice to one of ordinary skill in the art practicing the invention at the time the invention was made to provide a result effect variable for the purification of a product, especially given the beneficial teachings of the prior before him or her.

Accordingly, the claimed invention was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, especially in the absence of evidence to the contrary.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-5, 8, 14-16 and 18-24 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over Claims 1-8, 10, 11 and 13-20 of copending Application No. 10/143,156. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims are no more than obvious variants of one another.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michele Flood whose telephone number is 571-272-0964. The examiner can normally be reached on 7:00 am - 3:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Terry McKelvey can be reached on 571-272-0775. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Michele C. Flood

MICHELE FLOOD
PRIMARY EXAMINER

Michele Flood
Primary Examiner
Art Unit 1655

MCF
November 26, 2007